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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,143	LORENCE ET AL.	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 19, 2007 has been entered.

Information Disclosure Statement

The information disclosure statement submitted 12/19/2007 has been considered by the Examiner.

Withdrawn Rejections

The rejection of claims 1-4, 6, 7, and 16-23 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a carcinoid tumor with the mesogenic strain MK107 of Newcastle Disease Virus (NDV), does not reasonably provide enablement for any replication-competent strain of NDV has been withdrawn in view of applicants' amendments to the claims and applicants' arguments.

The rejection of claims 13-15 as being provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 157-161, 163-170, 172, 174, 183, 196-219, and 230-232 of copending Application No. 09/958,809 has been withdrawn in view of amendments made to the copending claims.

Reinstated Rejections

Upon further consideration and search, previously withdrawn rejections under 35 U.S.C. §102 have been reinstated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-8, 13, 14, 16-19 and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Pecora et al. (Journal of Clinical Oncology, 2002, 20(9):2251-2266) as evidenced by Laurie et al. (Clin. Cancer Res., 2006, 12(8):2555-2562), Chandler et al. (American Journal of Surgery, 1965, 109:221-222), Martensson et al. (Journal of Surgical Oncology, 1984, 27:152-158), Drougas et al. (Am. J Surg., 1998,175:408-412) and Wessels et al. (Journal of Surgical Research, 2001, 95, 8–12).

Pecora et al. teaches that oncolytic NDV strains, including replication-competent PV701, administered intravenously (i.e., systemically), replicate selectively in human cancer cells implanted in athymic mice resulting in tumor regression (page 2251-introduction). Human patients with various tumor types (e.g., colorectal, pancreatic, renal, breast, lung, etc.) were also given PV701, which is mesogenic as evidenced by

Laurie et al. (page 2556 under heading Patients and Methods). The virus can be administered over one or more cycles where at least one cycle comprises one or more desensitizing does followed by one or more escalating does of a higher amount of virus (pages 2252-top of left column and 2253-under heading Desensitizing regimen). The desensitizing dose given was 1.2×10^{10} PFU per square meter of patient surface area and the escalating dose given was 2.4×10^{10}, 4.8×10^{10}, 7.2×10^{10}, 9.6×10^{10} or 1.44×10^{11} PFU per square meter of patient surface area (page 2253-under heading Desensitizing regimen).

Pecora et al. contemplates treating subjects with carcinoid tumors. This includes those subjects who also have carcinoid syndrome. (It is well known in the art that patients with carcinoid syndrome have carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, Pecora et al. will also treat the 10% or more of the subjects who also have carcinoid syndrome. Therefore, a person of ordinary skill in the art would recognize that treating carcinoid tumors with NDV, according to the method of Pecora et al., to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome as evidenced by Chandler et al. (resection of carcinoid tumors relieved carcinoid syndrome symptoms), Martensson et al. (embolization of hepatic carcinoid tumors relieved carcinoid syndrome symptoms), Drougas et al. (hepatic artery chemoembolization of carcinoid tumors relieved carcinoid syndrome symptoms) and Wessels et al. (radiofrequency ablation of carcinoid tumors relieved carcinoid syndrome symptoms).

Patients who were taking octreotide before tumor treatment to control carcinoid syndrome were able to reduce their octreotide dose or eliminate their octreotide dose after tumor treatment (see Wessels et al. abstract). Further, a reduction of tumor size or eliminating the tumors also reduced the levels of 5-hydroxyindole acetic acid (5-HIAA) in urine (see Martensson et al., abstract). Therefore, a person of ordinary skill in the art would recognize that treating carcinoid tumors by any means, including NDV, to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome in those subjects who have carcinoid syndrome, reduce the levels of 5-HIAA in urine, and reduce the need for octreotide.

Claims 1, 5-8, 11-14, 16-19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al. (WO 00/62735) as evidenced by Chandler et al. (American Journal of Surgery, 1965, 109:221-222), Martensson et al. (Journal of Surgical Oncology, 1984, 27:152-158), Drougas et al. (Am. J Surg., 1998,175:408-412) and Wessels et al. (Journal of Surgical Research, 2001, 95, 8–12).

Roberts et al. teaches a method of treating a neoplasm, which is defined to include tumors and cancer, in a mammal by administering a replication-competent RNA virus (page 7, lines 4-8; pages 31-32; and Examples). Roberts et al. also discloses using a mesogenic strain of NDV (MK107) that selectively kills tumor cells (page 17, line 24 to page 18, line 26 and the Examples, especially Example 15). NDV is a Paramyxovirus (page 18, lines 6-15). The virus can be administered systemically or intravenously (page 33, lines 17 and 26), and the virus can be administered over the

course of 4 minutes to 24 hours or 20 to 60 minutes (page 36, lines 16-19). The virus can be administered over one or more cycles where at least one cycle comprises one or more desensitizing doses followed by one or more escalating doses of a higher amount of virus (pages 34-35 and the Examples, especially Example 20). The desensitizing dose can be at least 1.2×10^{10} PFU per square meter of patient surface area (page 35, line 17) and the escalating dose can be at least 2.4×10^{10} PFU per square meter of patient surface area (page 35, line 20). The subject can be human (page 65 and Example 20) or non-human (Examples 2-9), and after treating the subject, the size of the tumor decreases (page 32, lines 18-22 and Example 20).

Roberts et al. contemplates treating subjects with carcinoid tumors. This includes those subjects who also have carcinoid syndrome (It is well known in the art that patients with carcinoid syndrome have carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, Roberts et al. will also treat the 10% or more of the subjects who also have carcinoid syndrome. Therefore, a person of ordinary skill in the art would recognize that treating carcinoid tumors with NDV, according to the method of Roberts et al., to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome as evidenced by Chandler et al. (resection of carcinoid tumors relieved carcinoid syndrome symptoms), Martensson et al. (embolization of hepatic carcinoid tumors relieved carcinoid syndrome symptoms), Drougas et al. (hepatic artery chemoembolization of carcinoid tumors relieved carcinoid syndrome symptoms) and

Wessels et al. (radiofrequency ablation of carcinoid tumors relieved carcinoid syndrome symptoms).

Patients who were taking octreotide before tumor treatment to control carcinoid syndrome were able to reduce their octreotide dose or eliminate their octreotide dose after tumor treatment (see Wessels et al. abstract). Further, a reduction of tumor size or eliminating the tumors also reduced the levels of 5-hydroxyindole acetic acid (5-HIAA) in urine (see Martensson et al., abstract). Therefore, a person of ordinary skill in the art would recognize that treating carcinoid tumors by any means, including NDV, to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome in those subjects who have carcinoid syndrome, reduce the levels of 5-HIAA in urine, and reduce the need for octreotide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 10 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pecora et al. or Roberts et al. as applied to claims 1, 5-8, 13, 14 and 16-18 above.

Pecora et al. teaches a desensitizing dose of 1.2×10^{10} PFU per square meter of patient surface area and escalating doses of 2.4×10^{10}, 4.8×10^{10}, 7.2×10^{10}, 9.6×10^{10} or 1.44×10^{11} PFU per square meter of patient surface area (page 2253-under heading Desensitizing regimen). In addition, Pecora et al. teaches rates of administration of 1.2×10^{9} PFU per square meter of patient surface area per minute for doses of 1.2×10^{10} per square meter of patient surface area and a rate of 5×10^{9} PFU per square meter of patient surface area per minute for doses greater than 1.2×10^{10} per square meter of patient surface area.

Roberts et al. teaches that the desensitizing dose can be at least 1.2×10^{10} PFU per square meter of patient surface area (page 35, line 17) and the escalating dose can be at least 2.4×10^{10} PFU per square meter of patient surface area (page 35, line 20).

Neither reference teaches the doses or administration times of claims 9, 10 and 15. However, it is well within the purview of one of ordinary skill in the art to optimize dosages as well as the administration times as recited in claims 9, 10 and 15.

According to section 2144.05 of the MPEP, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

A particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the doses and rates of Pecora et al. and Roberts et al. produced a recognized result (i.e., tumor regression). Therefore, determining other optimum or workable dosages and rates is routine experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-8 and 16-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 7, 19, 22-25 and 27 of US Patent No. 7,056,689 ("the '689 patent") in view of Pecora et al. (Journal of Clinical Oncology, 2002, 20(9):2251-2266) and as evidenced by Chandler et al. (American Journal of Surgery, 1965, 109:221-222), Martensson et al. (Journal of Surgical Oncology, 1984, 27:152-158), Drougas et al. (Am. J Surg., 1998,175:408-412) and Wessels et al. (Journal of Surgical Research, 2001, 95, 8–12). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating cancer in a mammal by administering a negative-stranded RNA virus.

The instant claims are drawn to a method for treating a mammalian subject having a carcinoid tumor and carcinoid syndrome, comprising administering to the subject an amount of a therapeutic virus effective to treat the tumor and decrease one or more symptoms of the carcinoid syndrome, wherein the virus is a Newcastle Disease virus (NDV).

The patented claims are drawn to a method of treating cancer in a mammal having a tumor comprising administering intravenously to said mammal more than one dose of a pharmaceutical composition comprising live purified NDV in an amount sufficient to cause tumor regression

Pecora et al. teaches that oncolytic NDV strains, including replication-competent PV701, administered intravenously (i.e., systemically), replicate selectively in human cancer cells resulting in tumor regression (page 2251-introduction). Human patients with various tumor types (e.g., colorectal, pancreatic, renal, breast, lung, carcinoid, etc.) were also given PV701, which is a mesogenic strain of NDV.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by the '689 patent to also treat subjects with carcinoid tumors and carcinoid syndrome. One would have been motivated to do so given the suggestion by Pecora et al. to treat various malignancies with NDV. There would have been a reasonable expectation of success given the fact that Pecora et al. observed in seven patients with diverse malignancies (including mesothelioma, melanoma, colon carcinoma, breast carcinoma, pancreatic carcinoma, and carcinoid) measurable tumor reduction after treatment with NDV.

The '689 patent contemplates treating subjects with cancer/tumors, which encompasses carcinoid tumors. This also includes those subjects who have carcinoid syndrome (It is well known in the art that patients with carcinoid syndrome have carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, the '698 patent will also treat the 10% or more of the subjects who also have carcinoid

syndrome. Therefore, a person of ordinary skill in the art would recognize that treating carcinoid tumors with NDV, according to the method of the '689 patent, to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome as evidenced by Chandler et al. (resection of carcinoid tumors relieved carcinoid syndrome symptoms), Martensson et al. (embolization of hepatic carcinoid tumors relieved carcinoid syndrome symptoms), Drougas et al. (hepatic artery chemoembolization of carcinoid tumors relieved carcinoid syndrome symptoms) and Wessels et al. (radiofrequency ablation of carcinoid tumors relieved carcinoid syndrome symptoms).

Thus, the patented claims and the instant claims are not patentably distinct.

Claims 1-8, 13, 16, and 17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-8, 50, 51, 63-65, 69, 70, 73, 115-120, 132, 134, 136, and 144 of copending Application No. 10/167652 ("the '652 application") in view of Pecora et al. (Journal of Clinical Oncology, 2002, 20(9):2251-2266). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating cancer by administering a replication competent, interferon sensitive clonal RNA virus to a mammal. The carcinoid tumor of the instant application is within the breadth of the term neoplasm, which is recited in the '652 application claims (see claims 7, 50 and 51 (solid tumor)). In addition, treating a

neoplasm or solid tumor in a mammal with a virus will obviously, at the same time, infect the neoplasm or tumor.

Pecora et al. teaches that oncolytic NDV strains, including replication-competent PV701, administered intravenously (i.e., systemically), replicate selectively in human cancer cells implanted in athymic mice resulting in tumor regression (page 2251-introduction). Human patients with various tumor types (e.g., colorectal, pancreatic, renal, breast, lung, carcinoid, etc.) were also given PV701, which is a mesogenic strain of Newcastle Disease Virus (NDV).

It would have been obvious to one of ordinary skill in the art to modify the methods taught by the '652 application to also treat subjects with carcinoid tumors and carcinoid syndrome. One would have been motivated to modify the methods taught by the '652 application given the suggestion by Pecora et al. to treat various malignancies with NDV. There would have been a reasonable expectation of success given the fact that Pecora et al. observed in seven patients with diverse malignancies (including mesothelioma, melanoma, colon carcinoma, breast carcinoma, pancreatic carcinoma, and carcinoid) measurable tumor reduction after treatment with NDV.

The '652 application contemplates treating subjects with solid tumors, which encompasses carcinoid tumors. This also includes those subjects who have carcinoid syndrome (It is well known in the art that patients with carcinoid syndrome have carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, the '652 application will also treat the 10% or more of the subjects who also have carcinoid syndrome. Therefore, a person of ordinary skill in the art would recognize that

infecting solid tumors, e.g., carcinoid tumors, with NDV according to the method of the '652 application will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome.

Thus, the copending claims and the instant claims are not patentably distinct.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 12, 17, 21, 22, 26-28 and 34 of copending Application No. 10/518,732 ("the '732 application"). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The copending claims are drawn to a method for administering a therapeutic virus to a subject in one or more cycles, wherein at least one cycle comprises administering sequentially two or more desensitization doses of the virus followed by administering one or more escalated doses of the virus, wherein:

the virus is a negative-stranded RNA virus;

the amount of the virus in the second and any subsequent desensitization dose is not less than the amount of the virus in the preceding desensitization dose; and the amount of the virus in each of the one or more escalated doses is higher than the amount of virus in each of the desensitization doses, wherein the virus is a mesogenic strain of Newcastle Disease Virus.

The instant claims are drawn to a method for treating a mammalian subject having a carcinoid tumor and carcinoid syndrome, comprising administering to the

subject an amount of a therapeutic virus effective to treat the tumor and decrease one or more symptoms of the carcinoid syndrome, wherein the virus is a mesogenic strain of Newcastle Disease virus, wherein the virus is administered intravenously, wherein the therapeutic virus is administered to the subject in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by administering one or more escalated doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose.

The administration methods are the same, and thus, not patentably distinct.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/547,654 ("the '654 application") in view of Pecora et al. (Journal of Clinical Oncology, 2002, 20(9):2251-2266) and as evidenced by Chandler et al. (American Journal of Surgery, 1965, 109:221-222), Martensson et al. (Journal of Surgical Oncology, 1984, 27:152-158), Drougas et al. (Am. J Surg., 1998,175:408-412) and Wessels et al. (Journal of Surgical Research, 2001, 95, 8–12). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to treating a subject having a tumor by administering NDV in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by

administering one or more escalated doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose.

The instant claims are drawn to a method for treating a mammalian subject having a carcinoid tumor and carcinoid syndrome, comprising administering to the subject an amount of a therapeutic virus effective to treat the tumor and decrease one or more symptoms of the carcinoid syndrome, wherein the virus is a mesogenic strain of Newcastle Disease virus, wherein the virus is administered intravenously, wherein the therapeutic virus is administered to the subject in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by administering one or more escalated doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose.

The claims of the '654 application are drawn to a method for treating a mammalian subject having a tumor, comprising administering to the subject an amount of a Newcastle disease virus effective to treat the subject, wherein

the virus is administered to the subject in one or more cycles;

at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by one or more escalated doses of the virus to the subject;

the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose; and

the first escalated dose is administered from 18 to 36 hours after the first desensitization dose. The virus is a mesogenic strain of NDV.

Pecora et al. teaches that oncolytic NDV strains, including replication-competent PV701, administered intravenously (i.e., systemically), replicate selectively in human cancer cells implanted in athymic mice resulting in tumor regression (page 2251-introduction). Human patients with various tumor types (e.g., colorectal, pancreatic, renal, breast, lung, carcinoid, etc.) were also given PV701, which is a mesogenic strain of Newcastle Disease Virus (NDV).

It would have been obvious to one of ordinary skill in the art to modify the treatment method taught by the '654 application to also treat subjects with carcinoid tumors and carcinoid syndrome. One would have been motivated to do so given the suggestion by Pecora et al. to treat various malignancies including carcinoid tumors with NDV. There would have been a reasonable expectation of success given the fact that Pecora et al. observed in seven patients with diverse malignancies (including mesothelioma, melanoma, colon carcinoma, breast carcinoma, pancreatic carcinoma, and carcinoid) measurable tumor reduction after treatment with NDV.

The '654 application contemplates treating subjects with tumors, which encompasses carcinoid tumors. This also includes those subjects who have carcinoid syndrome (It is well known in the art that patients with carcinoid syndrome have carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, the '654 application will also treat the 10% or more of the subjects who also have carcinoid syndrome. Therefore, a person of ordinary skill in the art would recognize that

treating carcinoid tumors with NDV, according to the method of the '654 application, to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome as evidenced by Chandler et al. (resection of carcinoid tumors relieved carcinoid syndrome symptoms), Martensson et al. (embolization of hepatic carcinoid tumors relieved carcinoid syndrome symptoms), Drougas et al. (hepatic artery chemoembolization of carcinoid tumors relieved carcinoid syndrome symptoms) and Wessels et al. (radiofrequency ablation of carcinoid tumors relieved carcinoid syndrome symptoms).

Thus, the copending claims and the instant claims are not patentably distinct.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/548,057 ("the '057 application") in view of Pecora et al. (Journal of Clinical Oncology, 2002, 20(9):2251-2266) and as evidenced by Chandler et al. (American Journal of Surgery, 1965, 109:221-222), Martensson et al. (Journal of Surgical Oncology, 1984, 27:152-158), Drougas et al. (Am. J Surg., 1998,175:408-412) and Wessels et al. (Journal of Surgical Research, 2001, 95, 8–12). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to treating a subject having a tumor by administering NDV in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by

administering one or more escalated doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose.

The instant claims are drawn to a method for treating a mammalian subject having a carcinoid tumor and carcinoid syndrome, comprising administering to the subject an amount of a therapeutic virus effective to treat the tumor and decrease one or more symptoms of the carcinoid syndrome, wherein the virus is a mesogenic strain of Newcastle Disease virus, wherein the virus is administered intravenously, wherein the therapeutic virus is administered to the subject in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by administering one or more escalated doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose. The cycle comprises one desensitizing dose of from 1.2 X 10^{10} PFU to 4.8 X 10^{10} PFU per square meter of patient surface area, and one or more escalated doses of from 2.4 X 10^{10} PFU to 1.2 X 10^{11} PFU per square meter of patient surface area, and wherein the desensitization dose is about 2.4 X 10^{10} PFU per square meter of patient surface area, and the one or more escalated doses are about 4.8 X 10^{10} PFU per square meter of patient surface area.

The claims of the '057 application are drawn to a method for treating a mammalian subject having a tumor, comprising administering to the subject an amount of a Newcastle disease virus effective to treat the subject, wherein

the virus is administered to the subject in one or more cycles;

at least one cycle comprises administering sequentially one or more initial doses of from 1.8×10^8 PFU to 4.8×10^{10} PFU of the virus per square meter of the patient surface area followed by administering one or more subsequent doses of from 2.4×10^{10} PFU to 1.2×10^{11} PFU 7.2×10^{10} of the virus per square meter of patient surface area. The virus is a mesogenic strain of NDV.

Pecora et al. teaches that oncolytic NDV strains, including replication-competent PV701, administered intravenously (i.e., systemically), replicate selectively in human cancer cells implanted in athymic mice resulting in tumor regression (page 2251-introduction). Human patients with various tumor types (e.g., colorectal, pancreatic, renal, breast, lung, carcinoid, etc.) were also given PV701, which is a mesogenic strain of Newcastle Disease Virus (NDV).

It would have been obvious to one of ordinary skill in the art to modify the treatment method taught by the '057 application to also treat subjects with carcinoid tumors and carcinoid syndrome. One would have been motivated to do so given the suggestion by Pecora et al. to treat various malignancies including carcinoid tumors with NDV. There would have been a reasonable expectation of success given the fact that Pecora et al. observed in seven patients with diverse malignancies (including mesothelioma, melanoma, colon carcinoma, breast carcinoma, pancreatic carcinoma, and carcinoid) measurable tumor reduction after treatment with NDV.

The '057 application contemplates treating subjects with tumors, which encompasses carcinoid tumors. This also includes those subjects who have carcinoid syndrome (It is well known in the art that patients with carcinoid syndrome have

carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, the '654 application will also treat the 10% or more of the subjects who also have carcinoid syndrome. Therefore, a person of ordinary skill in the art would recognize that treating carcinoid tumors with NDV, according to the method of the '057 application, to reduce the size of or eliminate the tumors will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome as evidenced by Chandler et al. (resection of carcinoid tumors relieved carcinoid syndrome symptoms), Martensson et al. (embolization of hepatic carcinoid tumors relieved carcinoid syndrome symptoms), Drougas et al. (hepatic artery chemoembolization of carcinoid tumors relieved carcinoid syndrome symptoms) and Wessels et al. (radiofrequency ablation of carcinoid tumors relieved carcinoid syndrome symptoms).

Thus, the copending claims and the instant claims are not patentably distinct.

Claims 1, 5-8 and 16-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14, 17, 18, 21, 22, 33, 34, 36-39, and 41 of copending Application No. 11/441,201 in view of Pecora et al. (Journal of Clinical Oncology, 2002, 20(9):2251-2266). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating a tumor by administering NDV to a mammal.

Pecora et al. teaches that oncolytic NDV strains, including replication-competent PV701, administered intravenously (i.e., systemically), replicate selectively in human

cancer cells implanted in athymic mice resulting in tumor regression (page 2251-introduction). Human patients with various tumor types (e.g., colorectal, pancreatic, renal, breast, lung, carcinoid, etc.) were also given PV701, which is a mesogenic strain of Newcastle Disease Virus (NDV).

It would have been obvious to one of ordinary skill in the art to modify the methods taught by the '201 application to also treat subjects with carcinoid tumors and carcinoid syndrome. One would have been motivated to modify the methods taught by the '201 application given the suggestion by Pecora et al. to treat various malignancies with NDV. There would have been a reasonable expectation of success given the fact that Pecora et al. observed in seven patients with diverse malignancies (including mesothelioma, melanoma, colon carcinoma, breast carcinoma, pancreatic carcinoma, and carcinoid) measurable tumor reduction after treatment with NDV.

The '201 application contemplates treating subjects with tumors, which encompasses carcinoid tumors. This also includes those subjects who have carcinoid syndrome (It is well known in the art that patients with carcinoid syndrome have carcinoid tumors). By treating a population of subjects with carcinoid tumors with NDV, the '201 application will also treat the 10% or more of the subjects who also have carcinoid syndrome. Therefore, a person of ordinary skill in the art would recognize that infecting solid tumors, e.g., carcinoid tumors, with NDV according to the method of the '201 application will inherently reduce or treat carcinoid syndrome symptoms in those subjects who have carcinoid syndrome.

Thus, the copending claims and the instant claims are not patentably distinct.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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